

AMENDMENT AND RESPONSE UNDER 37 CFR § 1.116 – EXPEDITED PROCEDURE

AND RESPONSE TO ADVISORY ACTION

Serial Number: 10/615,484

Filing Date: July 8, 2003

Title: THERAPEUTIC AND DIAGNOSTIC COMPOUNDS, COMPOSITIONS, AND METHODS

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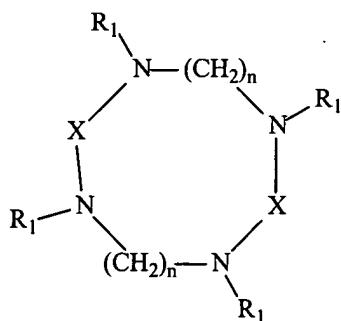
Dkt: 295.034US1

In the Claims

Please amend the claims as follows:

1. (Original) A complex comprising:

a) compound of formula (I):

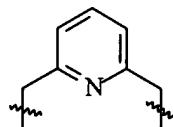


(I)

wherein:

each R<sub>1</sub> is independently hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, optionally substituted with carboxy;

each X is independently (CH<sub>2</sub>)<sub>n</sub> or



and each n is independently 2, 3, or 4;

wherein the compound of formula I is substituted on one or more carbons other than a carbon of R<sub>1</sub> with one or more groups -Y(PO<sub>3</sub>H<sub>2</sub>)<sub>m</sub>; wherein Y is a linker group; and m is 1, 2, 3, 4, 5, or 6; or a pharmaceutically acceptable salt thereof; and

b) a detectable or therapeutic radionuclide.

2. (Original) The complex of claim 1 wherein each R<sub>1</sub> is independently (C<sub>1</sub>-C<sub>4</sub>)alkyl, substituted with carboxy.

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3. (Original) The complex of claim 1 wherein each R<sub>1</sub> is carboxymethyl or 2-carboxyethyl.
4. (Original) The complex of claim 1 wherein each R<sub>1</sub> is carboxymethyl.
5. (Original) The complex of claim 1 wherein each n is independently 2 or 3.
6. (Original) The complex of claim 1 wherein each n is 2.
7. (Original) The complex of claim 1 wherein the linker group Y is about 5 angstroms to about 100 angstroms in length.
8. (Original) The complex of claim 1 wherein the linker group Y is about 10 angstroms to about 50 angstroms in length.
9. (Original) The complex of claim 1 wherein the compound of formula I is substituted on a carbon other than a carbon of R<sub>1</sub> with one or two groups -Y(PO<sub>3</sub>H<sub>2</sub>)<sub>m</sub>, wherein m is 1, 2, 3, 4, 5, or 6.
10. (Original) The complex of claim 1 wherein the linker group Y is an amino acid, a peptide, a saccharide, or a divalent (C<sub>1</sub>-C<sub>10</sub>)alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N(R<sub>d</sub>)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R<sub>d</sub> is hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl.
11. (Original) The complex of claim 10 wherein the linker group Y is an amino acid.
12. (Original) The complex of claim 11 wherein the amino acid is non-lipophilic.

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13. (Original) The complex of claim 10 wherein the linker group Y is a saccharide.
14. (Original) The complex of claim 13 wherein the saccharide is a monosaccharide, disaccharide, or trisaccharide.
15. (Original) The complex of claim 13 wherein the saccharide is a polysaccharide.
16. (Original) The complex of claim 10 wherein the linker group Y is a peptide.
17. (Original) The complex of claim 16 wherein the peptide comprises 2 to 25 amino acid residues.
18. (Original) The complex of claim 17 wherein the amino acid residues are non-lipophilic.
19. (Original) The complex of claim 10 wherein the linker group Y is a divalent ( $C_1-C_{10}$ )alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N( $R_d$ )-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein  $R_d$  is hydrogen or ( $C_1-C_4$ )alkyl.
20. (Original) The complex of claim 10 wherein the linker group Y is a divalent ( $C_1-C_{10}$ )alkyl chain, comprising one or more non-peroxide oxy (-O-), -N( $R_d$ )-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein  $R_d$  is hydrogen or ( $C_1-C_4$ )alkyl.
21. (Original) The complex of claim 10 wherein the linker group Y is a divalent ( $C_1-C_{10}$ )alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N( $R_d$ )-, or divalent aryl within the chain or at the terminus of the chain, which chain is substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein  $R_d$  is hydrogen or ( $C_1-C_4$ )alkyl.

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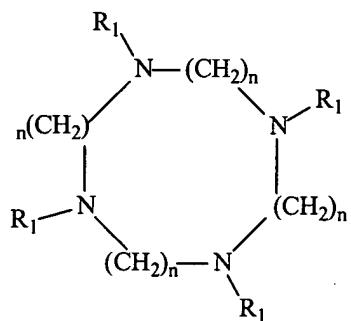
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22. (Original) The complex of claim 10 wherein the linker group Y is a divalent ( $C_1-C_{10}$ )alkyl chain comprising one or more non-peroxide oxy (-O-), -N( $R_d$ )-, or divalent aryl within the chain or at the terminus of the chain, which chain is substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein  $R_d$  is hydrogen or ( $C_1-C_4$ )alkyl.

23. (Original) The complex of claim 1 wherein each  $-Y(PO_3H_2)_m$  is independently 4-[2-(Bis-phosphonomethyl-amino)-acetylamino]-benzyl; 4-[4-(Bis-phosphonomethyl-carbamoyl)-butyrylamino]-benzyl; 4-(3,3-Bis-phosphono-propionylamino)-benzyl; 4-[4-(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-butyrylamino]-benzyl; 4-(3-[2-(Bis-phosphonomethyl-amino)-acetylamino]-2-{{[2-(bis-phosphonomethyl-amino)-acetylamino]-methyl}-propionylamino}-benzyl; 4-(4-{Bis-[(bis-phosphonomethyl-carbamoyl)-methyl]-carbamoyl}-butyrylamino)-benzyl; 4-{3-(3,3-Bis-phosphono-propionylamino)-2-[(3,3-bis-phosphono-propionylamino)-methyl]-[propionylamino]-benzyl; 4-(4-{Bis-[(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-methyl]-carbamoyl}-butyrylamino)-benzyl; 4-{4-[(Bis-phosphono-methyl)-carbamoyl]-butyrylamino}-benzyl; or 4-[4-(Bis-{{(bis-phosphono-methyl)-carbamoyl]-methyl}-carbamoyl}-butyrylamino]-benzyl.

24. (Original) The complex of claim 1 wherein the compound of formula I is a compound of formula (II):



(II)

wherein:

each R<sub>1</sub> is independently hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, optionally substituted with carboxy (COOH); and each n is independently 2, 3, or 4; wherein the compound of formula (II) is substituted on one or more carbons other than a carbon of R<sub>1</sub> with one or more groups -Y(PO<sub>3</sub>H<sub>2</sub>)<sub>m</sub>; wherein Y is a linker group; and m is 1, 2, 3, 4, 5, or 6; or a pharmaceutically acceptable salt thereof.

25. (Original) The complex of claim 24 wherein each R<sub>1</sub> is independently (C<sub>1</sub>-C<sub>4</sub>)alkyl, substituted with carboxy.

26. (Original) The complex of claim 24 wherein each R<sub>1</sub> is carboxymethyl.

27. (Original) The complex of claim 24 wherein the compound of formula II is substituted on a carbon other than a carbon of R<sub>1</sub> with one or two groups -Y(PO<sub>3</sub>H<sub>2</sub>)<sub>m</sub>.

28. (Original) The complex of claim 24 wherein the compound of formula II is substituted on carbon with one group -Y(PO<sub>3</sub>H<sub>2</sub>)<sub>m</sub>.

29. (Original) The complex of claim 24 wherein the linker group Y is an amino acid, a peptide, a saccharide, or a divalent (C<sub>1</sub>-C<sub>10</sub>)alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N(R<sub>d</sub>)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R<sub>d</sub> is hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl.

30. (Original) The complex of claim 24 wherein the linker group Y is a divalent (C<sub>1</sub>-C<sub>10</sub>)alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N(R<sub>d</sub>)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on

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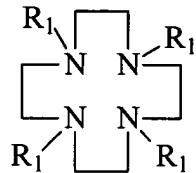
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carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R<sub>d</sub> is hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl.

31. (Original) The complex of claim 24 wherein each -Y(PO<sub>3</sub>H<sub>2</sub>)<sub>m</sub> is independently 4-[2-(Bis-phosphonomethyl-amino)-acetylamino]-benzyl; 4-[4-(Bis-phosphonomethyl-carbamoyl)-butyrylamino]-benzyl; 4-(3,3-Bis-phosphono-propionylamino)-benzyl; 4-[4-(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-butyrylamino]-benzyl; 4-(3-[2-(Bis-phosphonomethyl-amino)-acetylamino]-2-{{[2-(bis-phosphonomethyl-amino)-acetylamino]-methyl}-propionylamino}-benzyl; 4-{4-[(bis-phosphonomethyl-carbamoyl)-methyl]-carbamoyl}-butyrylamino)-benzyl; 4-{3-(3,3-Bis-phosphono-propionylamino)-2-[(3,3-bis-phosphono-propionylamino)-methyl]-[propionylamino]-benzyl; 4-{4-[(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-methyl]-carbamoyl}-butyrylamino)-benzyl; 4-{4-[(Bis-phosphono-methyl)-carbamoyl]-butyrylamino}-benzyl; or 4-[4-(Bis-{{(bis-phosphono-methyl)-carbamoyl]-methyl}-carbamoyl}-butyrylamino]-benzyl.

32. (Original) The complex of claim 1 wherein the compound of formula I is a compound of formula III:



(III)

wherein:

each R<sub>1</sub> is independently hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, optionally substituted with carboxy (COOH); and wherein the compound of formula III is substituted on one or more carbons other than a carbon of R<sub>1</sub> with one or more groups -Y(PO<sub>3</sub>H<sub>2</sub>)<sub>m</sub>; wherein Y is a linker group; and m is 1, 2, 3, 4, 5, or 6; or a pharmaceutically acceptable salt thereof.

33. (Original) The complex of claim 32 wherein each R<sub>1</sub> is independently (C<sub>1</sub>-C<sub>4</sub>)alkyl, substituted with carboxy.

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34. (Original) The complex of claim 32 wherein each R<sub>1</sub> is carboxymethyl.

35. (Original) The complex of claim 32 wherein the compound of formula III is substituted with one or two groups -Y(PO<sub>3</sub>H<sub>2</sub>)<sub>m</sub>.

36. (Original) The complex of claim 32 wherein the compound of formula III is substituted with one group -Y(PO<sub>3</sub>H<sub>2</sub>)<sub>m</sub>.

37. (Original) The complex of claim 32 wherein the linker group Y is an amino acid, a peptide, a saccharide, or a divalent (C<sub>1</sub>-C<sub>10</sub>)alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N(R<sub>d</sub>)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R<sub>d</sub> is hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl.

38. (Original) The complex of claim 32 wherein the linker group Y is a divalent (C<sub>1</sub>-C<sub>10</sub>)alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N(R<sub>d</sub>)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R<sub>d</sub> is hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl.

39. (Original) The complex of claim 32 wherein each -Y(PO<sub>3</sub>H<sub>2</sub>)<sub>m</sub> is independently 4-[2-(Bis-phosphonomethyl-amino)-acetylamino]-benzyl; 4-[4-(Bis-phosphonomethyl-carbamoyl)-butyrylamino]-benzyl; 4-(3,3-Bis-phosphono-propionylamino)-benzyl; 4-[4-(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-butyrylamino]-benzyl; 4-(3-[2-(Bis-phosphonomethyl-amino)-acetylamino]-2-{[2-(bis-phosphonomethyl-amino)-acetylamino]-methyl}-propionylamino)-benzyl; 4-(4-{Bis-[(bis-phosphonomethyl-carbamoyl)-methyl]-carbamoyl}-butyrylamino)-benzyl; 4-{3-(3,3-Bis-phosphono-propionylamino)-2-[(3,3-bis-phosphono-propionylamino)-methyl]-[propionylamino]}-benzyl; 4-(4-{Bis-[(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-

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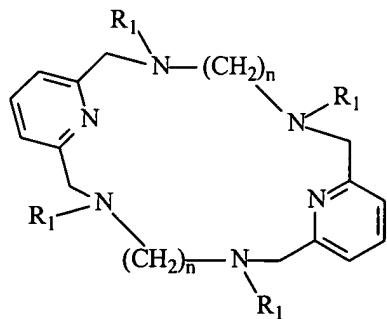
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methyl]-carbamoyl}-butyrylamino)-benzyl; 4-{4-[(Bis-phosphono-methyl)-carbamoyl]-butyrylamino}-benzyl; or 4-[4-(Bis-{[(bis-phosphono-methyl)-carbamoyl]-methyl}-carbamoyl)-butyrylamino]-benzyl.

40. (Original) The complex of claim 32 wherein each R<sub>1</sub> is independently (C<sub>1</sub>-C<sub>4</sub>)alkyl, substituted with carboxy (COOH); and wherein the ring is substituted on carbon with a group - Y(PO<sub>3</sub>H<sub>2</sub>)<sub>m</sub>; or a pharmaceutically acceptable salt thereof.

41. (Original) The complex of claim 1 wherein the compound of formula I is a compound of formula IV:



(IV)

wherein:

each R<sub>1</sub> is independently hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, optionally substituted with carboxy (COOH); and each n is independently 2, 3, or 4; wherein the compound of formula IV is substituted on one or more carbons other than a carbon of R<sub>1</sub> with one or more groups - Y(PO<sub>3</sub>H<sub>2</sub>)<sub>m</sub>; wherein Y is a linker group; and m is 1, 2, 3, 4, 5, or 6; or a pharmaceutically acceptable salt thereof.

42. (Original) The complex of claim 41 wherein each R<sub>1</sub> is independently (C<sub>1</sub>-C<sub>4</sub>)alkyl, substituted with carboxy.

43. (Original) The complex of claim 41 wherein each R<sub>1</sub> is carboxymethyl.

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44. (Original) The complex of claim 41 wherein the compound of formula IV is substituted with one or two groups -Y(PO<sub>3</sub>H<sub>2</sub>)<sub>m</sub>.

45. (Original) The complex of claim 41 wherein the compound of formula IV is substituted with one group -Y(PO<sub>3</sub>H<sub>2</sub>)<sub>m</sub>.

46. (Original) The complex of claim 41 wherein the linker group Y is an amino acid, a peptide, a saccharide, or a divalent (C<sub>1</sub>-C<sub>10</sub>)alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N(R<sub>d</sub>)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R<sub>d</sub> is hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl.

47. (Original) The complex of claim 41 wherein the linker group Y is a divalent (C<sub>1</sub>-C<sub>10</sub>)alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N(R<sub>d</sub>)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R<sub>d</sub> is hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl.

48. (Original) The complex of claim 41 wherein each -Y(PO<sub>3</sub>H<sub>2</sub>)<sub>m</sub> is independently 4-[2-(Bis-phosphonomethyl-amino)-acetylamino]-benzyl; 4-[4-(Bis-phosphonomethyl-carbamoyl)-butyrylamino]-benzyl; 4-(3,3-Bis-phosphono-propionylamino)-benzyl; 4-[4-(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-butyrylamino]-benzyl; 4-(3-[2-(Bis-phosphonomethyl-amino)-acetylamino]-2-{[2-(bis-phosphonomethyl-amino)-acetylamino]-methyl}-propionylamino)-benzyl; 4-(4-{Bis-[(bis-phosphonomethyl-carbamoyl)-methyl]-carbamoyl}-butyrylamino)-benzyl; 4-{3-(3,3-Bis-phosphono-propionylamino)-2-[(3,3-bis-phosphono-propionylamino)-methyl]-[propionylamino]-benzyl; 4-(4-{Bis-[(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-methyl]-carbamoyl}-butyrylamino)-benzyl; 4-{4-[(Bis-phosphono-methyl)-carbamoyl]-

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butyrylamino}-benzyl; or 4-[4-{[(bis-phosphono-methyl)-carbamoyl]-methyl}-carbamoyl]-butyrylamino]-benzyl.

49. (Original) The complex of claim 1 wherein the compound of formula I is  
(6-{4-[2-(Bis-phosphonomethyl-amino)-acetylamino]-benzyl}-4,7,10-tris-carboxymethyl-  
1,4,7,10-tetraaza-cyclododec-1-yl)-acetic acid;  
(6-{4-[4-(Bis-phosphonomethyl-carbamoyl)-butyrylamino]-benzyl}-4,7,10-tris-carboxymethyl-  
1,4,7,10-tetraaza-cyclododec-1-yl)-acetic acid;  
{3-[4-(3,3-Bis-phosphono-propionylamino)-benzyl]-4,7,10-tris-carboxymethyl-1,4,7,10-tetraaza-  
cyclododec-1-yl}-acetic acid;  
(4,7,10-Tris-carboxymethyl-3-{4-[4-(3-hydroxy-3,3-bis-phosphonopropyl-carbamoyl)-  
butyrylamino]-benzyl}-1,4,7,10-tetraaza-cyclododec-1-yl)-acetic acid;  
{3-[4-(3-[2-(Bis-phosphonomethyl-amino)-acetylamino]-2-{[2-(bis-phosphonomethyl-amino)-  
acetylamino]-methyl}-propionylamino)-benzyl]-4,7,10-tris-carboxymethyl-1,4,7,10tetraaza-  
cyclododec-1-yl}-acetic acid;  
{6-[4-(4-{Bis-[(bis-phosphonomethyl-carbamoyl)-methyl]-carbamoyl}-butyrylamino)-benzyl]-  
4,7,10-tris-carboxymethyl-1,4,7,10tetraaza-cyclododec-1-yl}-acetic acid;  
[3-(4-{3-(3,3-Bis-phosphono-propionylamino)-2-[(3,3-bis-phosphono-propionylamino)-methyl]-  
propionylamino}-benzyl)-4,7,10-tris-carboxymethyl-1,4,7,10tetraaza-cyclododec-1-yl]-acetic  
acid;  
{6-[4-(4-{Bis-[(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-methyl]-carbamoyl}-  
butyrylamino)-benzyl]-4,7,10-tris-carboxymethyl-1,4,7,10tetraaza-cyclododec-1-yl}-acetic acid;  
[6-(4-{4-[(Bis-phosphono-methyl)-carbamoyl]-butyrylamino}-benzyl)-4,7,10-tris-  
carboxymethyl-1,4,7,10tetraaza-cyclododec-1-yl]-acetic acid; or  
(6-{4-[4[(Bis-[(bis-phosphono-methyl)-carbamoyl]-methyl)-carbamoyl]-butyrylamino]-  
benzyl}-4,7,10-tris-carboxymethyl-1,4,7,10tetraaza-cyclododec-1-yl)-acetic acid.

50. (Original) The complex of claim 1 which comprises a detectable radionuclide.

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51. (Original) The complex of claim 50 wherein the detectable radionuclide is Technetium-99m, Ruthenium-97, Indium-111, Gallium-67 or -68, or Lead-203.

52. (Original) The complex of claim 1 which comprises a therapeutic radionuclide.

53. (Original) The complex of claim 52 wherein the therapeutic radionuclide is Holmium-166, Yttrium-90, Samarium-153, or Gadolinium-159.

54. (Original) The complex of claim 52 wherein the therapeutic radionuclide is Holmium-166.

55. (Original) A method for detecting the presence or absence of a calcified tissue target site within a mammal, comprising:

administering to the mammal a detectable dose of a complex of claim 50; and  
detecting the compound in the mammal to determine the presence or absence of the target site.

56. (Original) A therapeutic method for suppressing bone marrow in a mammal in need of such therapy comprising administering to the mammal, an effective bone marrow suppressing amount of a complex of claim 52.

57. (Original) A therapeutic method for treating cancer in a mammal in need of such therapy comprising administering to the mammal, an effective amount of a complex of claim 52.

58. (Original) A therapeutic method for treating bone pain in a mammal in need of such therapy comprising administering to the mammal, an effective amount of a complex of claim 52.

59. (Cancelled)

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60. (Currently Amended) A therapeutic method for treating a condition Crohn's disease, rheumatoid arthritis, multiple sclerosis, osteoporosis, osteopenia, osteomyelitis, Paget's disease, sickle cell anemia, or a lysosomal or peroxisomal storage disease treatable with stem cell transplantation, with or without stem cells comprising gene therapy, that utilizes bone marrow ablation, in a mammal in need of such therapy comprising administering to the mammal an effective amount of a complex of claim 52.

61. (Previously Presented) A therapeutic method for treating Crohn's disease, rheumatoid arthritis, multiple sclerosis, osteoporosis, osteopenia, osteomyelitis, Paget's disease, sickle cell anemia, or a lysosomal or peroxisomal storage disease, in a mammal in need of such therapy comprising administering to the mammal an effective amount of a complex of claim 52.

62. (Original) A pharmaceutical composition comprising the complex of claim 1 and a pharmaceutically acceptable carrier.

63. (Previously Presented) A therapeutic method for treating an infection in a mammal in need of such therapy comprising administering to the mammal, an effective amount of a complex of claim 52.